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(54) Title: A PROCESS FOR THE PREPARATION OF CITALOPRAM

(57) Abstract: A process for the preparation of Citalopram comprising the transformation of a compound of formula (VII), wherein R is C_1-C_4 alkyl. Compound (VII) is reacted in sequence with a Grignard reagent of a 4-halo fluorobenzene and a Grignard reagent of a 3-halo-N,N-dimethylpropylamine, respectively, giving a compound of formula (V), wherein R is as defined above. (V) Is hydrolysed to a compound of formula (IV), which is converted to a 5-oxime (III) by means of hydroxylamine, submitted to cyclization and converted to the corresponding 5-cyano derivative, i.e. Citalopram.

A PROCESS FOR THE PREPARATION OF CITALOPRAM

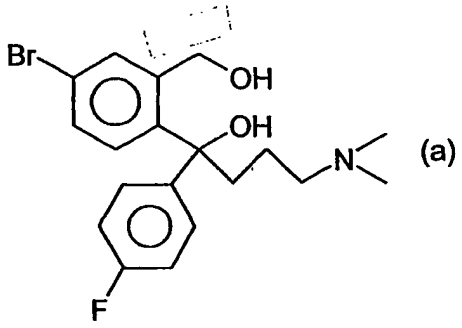
The present invention relates to a process for the preparation of Citalopram, 1-[3-(dimethylamino)propyl]-1-(4)-fluorophenyl)-1,3-dihydro-5-isobenzofurancarbonitrile, a well known antidepressant medicament.

BACKGROUND OF THE INVENTION

Citalopram and other 1-dimethylpropyl-1-phenylphthalanes (or 1-(3-dimethylpropyl)-1-phenyl-1,3-dihydroisobenzofurans) are described in US 4,136,193. Citalopram is endowed with antidepressant properties (J. Hyttel, Prog. Neuro-Psychopharmacol. & Biol. Psychiat., 1982, 6, 277-295 and A. Gravem, Acta Psychiatr. Scand., 1987, 75, 478-486).

EP-A-474580 also discloses the use of Citalopram in the treatment of dementia and cerebrovascular diseases.

US 4,136,193 describes a process for the preparation of Citalopram by cyclization of the compound of formula (a)



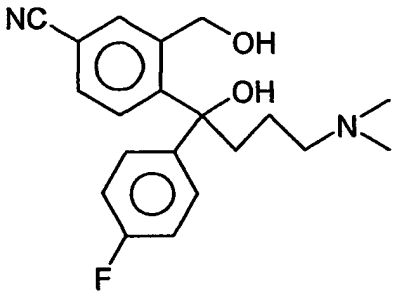
(a)

in the presence of a dehydrating agent, followed by replacement of the 5-bromo group with copper cyanide.

The starting material of formula (a) is obtained from 5-bromophthalide by means of two consecutive Grignard reactions with 4-fluorophenyl magnesium chloride and N,N-dimethylaminopropyl magnesium chloride, respectively.

A different process for the preparation of Citalopram is described in US

4,650,884, wherein an intermediate of formula (b)



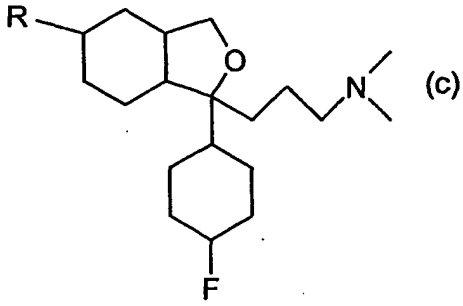
(b)

undergoes cyclization by dehydration with sulfuric acid.

The intermediate of formula (b) is prepared from 5-cyano-phthalide by means of two subsequent Grignard reactions with a 4-fluorophenyl magnesium halide and a N,N-dimethylamino propyl magnesium halide, respectively.

Methods for the preparation of the single enantiomers of Citalopram are reported in US 4,943,590, which also describes the cyclization of the intermediate of formula (b) in basic conditions.

WO 99/30548 discloses a novel synthetic process wherein a compound of formula (c),



(c)

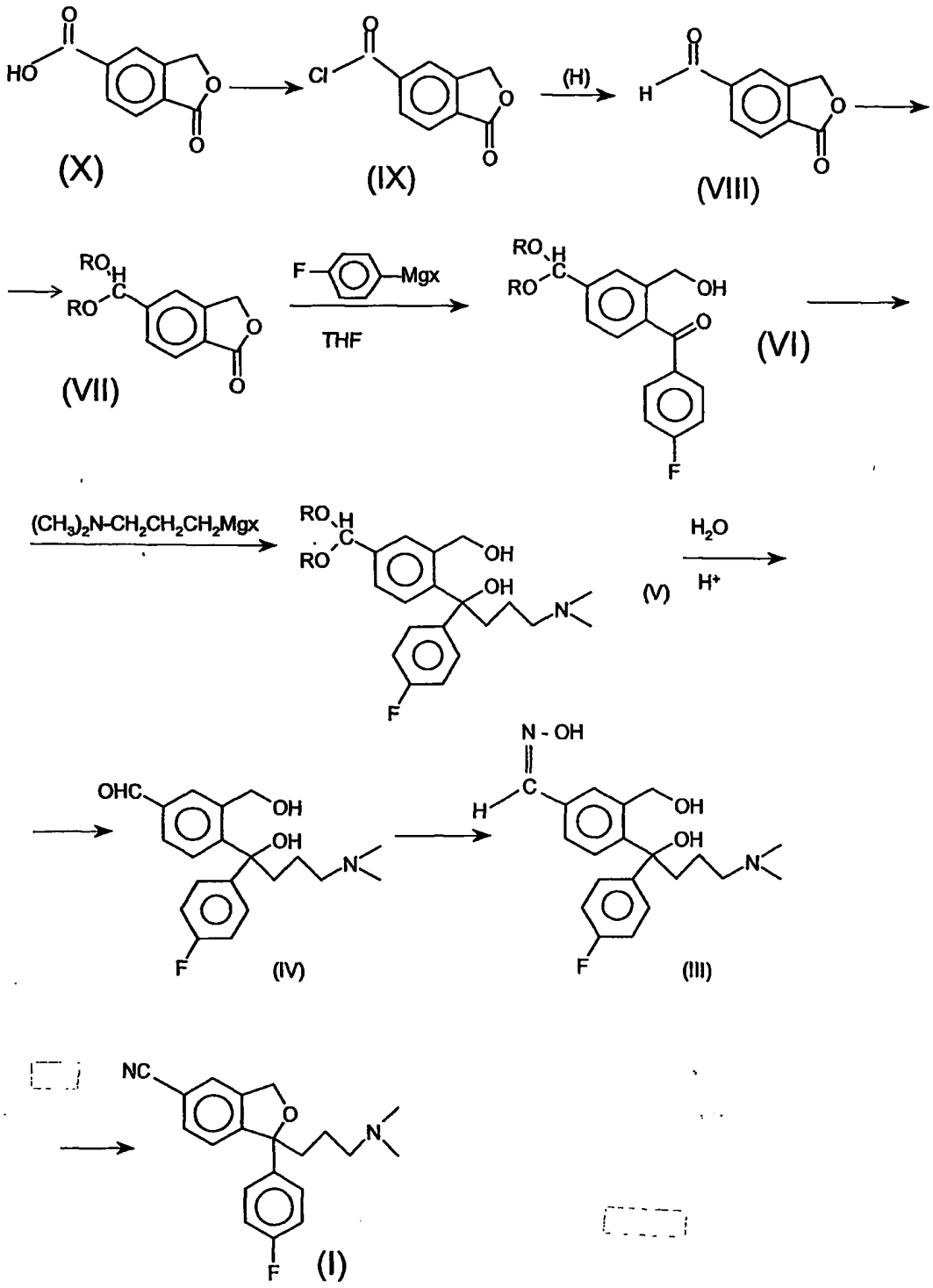
wherein R is a N,N-disubstituted amido group or a 4,5-dihydro-1,3-oxazol-2-yl group, is reduced with DIBAL-H (diisobutylaluminium hydride) to afford the 5-formyl intermediate. The subsequent conversion into 5-cyano group yields Citalopram.

The reduction step, which requires the use of metal hydrides such as DIBAL-H makes the process applicable with difficulty on industrial scale. This reaction in fact expansive and gives rise to safety problems, therefore it

is generally used only on laboratory scale.

SUMMARY OF THE INVENTION

It has now been found that Citalopram can be obtained in good yields by means of the process as claimed in claim 1, starting from a 5-formyl-phthalide acetal (VII), according to the following scheme, which also reports the preparation of the starting compound (VII).


(X)
(IX)
(H)
(VIII)
(VII)
THF
(VI)
(V)
(IV)
(III)
(I)

The 5-carboxyphtalide (X), used as the starting material, is known and commercially available [Tirouflet, J.; Bull. Soc. Sci. Bretagne, 26, 35 (1951)].

Compound (X) is transformed into the corresponding chloride (IX) by reaction with thionyl chloride, then is converted into the novel compound 5-formyl-phthalide of formula (VIII), in high yields and excellent purity.

The reduction can be carried out both by catalytic tecniques (reaction of ROSENMUND with H_2 and Pd/C catalyst in inert solvents, such as cyclohexane, toluene or xylene) and by chemical reductions with lithium or sodium and aluminium hydrides (lithium triterbutoxy aluminium hydride or RcD-Al).

After derivatisation of the formyl group as an acetal (compound VII, R = methyl or ethyl), two Grignard reactions are carried out in sequence:

- a first reaction with 4-fluorobenzyl magnesium chloride, bromide or iodide (preferably bromide);
- a second reaction with N,N-dimethylpropylamine 3-magnesium chloride, bromide or iodide (preferably chloride).

Isolation of the novel intermediate of formula (VI) can be avoided: in this case, the two Grignard reactions are carried out in sequence to obtain directly the intermediate of formula (V).

Likewise, the recovering and the purification of novel intermediates of formula (IV) and (III), obtained by hydrolysis of intermediate of formula (V) and transformation of the 5-formyl group (formula IV) into oxyimino group (formula III), can also be avoided.

The transformation of the 5-oxime group into 5-cyano group is a known reaction involving acetyloxyme formation followed by acetic acid elimination at high temperature.

The benzofuran ring closure of the compound of formula (III) can be accomplished both in inorganic acids, such as sulfuric or phosphoric acid, and

via formation of labile esters, such as methanesulfonyl, p-toluenesulfonyl, trifluoromethanesulfonyl ester, which are subsequently treated with bases, such as triethylamine, dimethylamine, pyridine in non alcoholic solvents, such as methylene chloride or tetrahydrofuran.

Surprisingly, the benzofuran ring closure by esterification and addition of bases leads at the same time to the transformation of the 5-oxime group into 5-cyano group, therefore allowing to convert in a single step the compound of formula (III) into Citalopram.

In all of the steps of the process of the present invention, the intermediates are obtained with satisfactory purity and good yields; moreover, the reaction conditions allow production on industrial scale, making the whole process economically competitive.

The compound of formula (I) can be used as free base or preferably as a salt with a pharmacologically acceptable acid (organic or inorganic).

The process of the invention can also be used for the preparation of the (S) enantiomer of Citalopram.

For this purpose, the compound of formula (III) is separated into the optically active enantiomers by a similar procedure to that described in US 4,943,590, to obtain the (S) enantiomer of the compound (III) which is then submitted to benzofuran ring closure according to the procedures described above.

The following examples illustrate the invention in further detail.

Example 1

5-Chlorocarboxy-phthalide

5-Carboxyphthalide (100 g, 0.56 mols) is suspended in toluene (600 ml). DMF (0.2 ml) and thionyl chloride (106.3 g, 0.89 mols) are added in sequence. The mixture is slowly heated under reflux for 3 hours.

300 ml of solvent are distilled off under atmospheric pressure and the mixture

is cooled under vigorous stirring at 25°C overnight. The crystallized product is filtered off, washed with toluene and dried to constant weight.

Yield: 90 g (82%).

Example 2

5-Formyl-phthalide

A solution of lithium triterbutoxy aluminium hydride (4.25 g, 0.0167 mols) in THF (15 ml) is dropped under nitrogen, at –78°C, into a solution of 5-chlorocarboxy phthalide (3 g, 0.0152 mols) in THF (15 ml), in 30 minutes and kept under stirring at –70°C for 90 minutes. Ethyl acetate is added (30 ml) and the mixture is slowly poured into a mixture of H_2O (5 ml), conc. HCl (5 ml), NaCl saturated solution (10 ml), precooled at +5°C.

After completion of the addition, the internal temperature is 15°C. The phases are separated and the organic layer is washed with acidulated water (50 ml), dried and concentrated to dryness. The residue (2.8 g) is chromatographed on SiO_2 eluting with a mixture of methylene chloride 98 : methanol 2 to give 0.5 g of pure product.

^{1}H-NMR ($CDCl_3$): 5.6 (2H, s), 8.05÷8.2 (3H, m), 10.2 (1H, s).

Elemental analysis for $C_9H_6O_3$:

Calculated: C = 66.67%; H = 3.73%

Found: C = 66.68%; H = 3.88%

m.p. = 158 ÷ 160°C

Example 3

5-Formyl-phthalide

5-Chlorocarbophthalide (75 g, 0.38 mols) is dissolved under stirring at 100°C in toluene (750 ml) and loaded into a hydrogenation reactor. Anhydrous sodium acetate (100 g; 1.14 mols), 10% anhydrous palladium over carbon catalyst (0.9 g), quinoline-S (0.5 ml) (J.W.Williams, Org. Syn, Call. Vol. 3, 629,1955) are added.

The reactor is washed with nitrogen and then pressurized at 4 bars with hydrogen.

The mixture is heated under stirring at 70°C for 4 hours, cooled to ambient temperature, transferred and heated again to 100°C, then filtered with suction. The recovered salts are washed with hot toluene (200 ml).

The organic phase is concentrated to 500 ml residue and kept at 10°C for 2 hours. The crystallized product is filtered, washed with a small amount of cold toluene and dried under vacuum to costant weight.

Yield = 43 g (70%); HPLC purity = 99%; m.p. = 160 ÷ 162°C.

Example 4

5-Formyl-phthalide-dimethylacetal

5-Formyl-phthalide (22 g; 0.1 mols) is suspended in methanol (220 ml), added wuth p-toluenesulfonic acid (2.2 g; 0.0115 mols) and heated to the internal temperature of 35°C for 3 hours. The mixture is filtered and the resulting solution is concentrated to dryness. Water is added (300 ml) and pH is adjusted to 8 with a bicarbonate saturated solution. After extraction with ethyl acetate (300 ml), the phases are separated and the organic layer is washed with water and a NaCl saturated solution, then dried.

The solution is concentrated to dryness and the residue is taken up with isopropyl alcohol (150 ml). After stirring at 15°C for 3 hours, the crystallized product is filtered and dried under vacuum to constant weight.

Yield = 20 g (71.5%)

^{1}H-NMR ($CDCl_3$): 3.3 (6H, S); 5.33 (2H, S); 5,55 (1H, S); 7.65 (2H, m); 7.9 (1H, d).

Elemental analysis for $C_{11}H_{12}O_4$:

Calculated: C = 63.45; H = 5.81

Found: C = 63.53; H = 5.94.

m.p. = 62 ÷ 64°C

Example 5

4[4-(Dimethylamino)-1-(4'fluorophenyl)-1-hydroxybutyl]-3-(hydroxy-methyl)-5-formylbenzene (formula IV).

A solution of 4-fluorophenyl magnesium bromide, prepared from 4-fluoro bromobenzene (30 g, 0.1 mols) and magnesium shavings (4.26 g, 0.177 mols) in anhydrous THF (150 ml) is slowly dropped into a solution of 5-formylphtalide dimethylacetal (20 g, 0.096 mols) in THF (130 ml) so as not to exceed 0°C.

After completion of the addition, the mixture is kept under stirring at 0 ÷ +5°C for 1 hour.

A second Grignard solution prepared from 3-dimethylpropyl chloride (18.6 g, 0.153 mols) and magnesium shavings (3.67 g, 0.153 mols) in anhydrous THF (70 ml) is poured in 1 hour into the reaction mixture, keeping the temperature under 10°C.

After completion of the addition, the mixture is stirred overnight at room temperature, then poured into an ammonium chloride saturated solution (200 ml). The phases are separated and the aqueous layer is extracted with ethyl acetate (150 ml). Methanol (100 ml), water (100 ml) and 6N HCl (300 ml) are added to the organic phase which is stirred for 30' at 25÷30°C, then concentrated under vacuum to half the volume, diluted with water (200 ml) and extracted with ethyl acetate (300 ml).

The aqueous phase is added with NH_4OH 25% to adjust pH to 10-10.5 and extracted again with ethyl acetate (2 x 200 ml each), dried with sodium sulfate and concentrated to dryness.

Yield = 28 g (60%); HPLC purity = 98%.

A sample is chromatographed over SiO_2 eluting with ethyl acetate 90: methanol 10, to obtain a standard for analysis having HPLC purity higher than 99%.

^{1}H-NMR ($CDCl_3$):1.62 and 1.72 (2H, AB); 2.25 (6H, s); 2.4 (2H, t); 2.38 and 2.47 (2H, AB); 4.3 and 4.5 (2H, AB); 6.95 (2H, t); 7.35 (2H, d.d.); 7.68 (1H, d); 7.82 (1H, d); 7.87 (1H, d); 10.05 (1H, s).

IR = n (cm-1) = 3340 (OH); 1693 (C = O); 1220 (C - F); 1086 (C - OH), 826 and 756 (aromatic).

Elemental analysis for: $C_{20}H_{24}NO_3F$

Calculated: C = 69.54%; H = 7%; N = 4.0%

Found: C = 68.75%; H = 7.18%; N = 3.99%

Example 6

4[4-(Dimethylamino)-1-(4-fluorophenyl)-1-hydroxybutyl]-3-(hydroxymethyl)-5-formylbenzene-oxime (formula III).

Compound (IV) (40 g, 0.116 mols) is dissolved in 95% ethanol (150 ml) and added with hydroxylamine HCl (15 g, 0.214 mols) in water (30 ml). After stirring for 30' at the internal temperature of 30°C, the mixture is diluted with water (300 ml), adjusted to pH 9.5 with 25% NH_4OH (30 ml), and extracted with ethyl acetate (2x ml 50). The organic phase is dried and concentrated.

Yield = 36 g (88%); HPLC purity = 98%

^{1}H-NMR [$(CD_3)_2CO$]: 1.6 (2H, m); 2.18 (6H, S); 2.25-2.35 (3H, m); 2.5-2.6 (1H, m); 2.8 (2H, m), 4.2 and 4.35 (2H, d.d.); 7.03 (2H, t); 7.4 (2H, d.d.); 7.55 (1H, d.d.); 7.65 (1H, d); 7.72 (1H, d); 7.15 (1H, S); 10.3 (1H, D_2O exchange).

Elemental analysis for $C_{20}H_{25}N_2O_3F$:

Calculated: C = 66.67; H= 6.94; N = 7.78

Found: C = 65.38; H = 7.54; N = 7.46

Example 7

1-(3-Dimethylpropyl)-1-(4-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile hydrobromide.

To a solution of 4-[4-(dimethylamino)-1-(4'-fluorophenyl)-1-

hidroxybutyl]-3-(hydroxymethyl)-5-formylbenzene-oxime (formula III), (20 g, 0.055 mols) in methylene chloride (ml 200), triethylamine (22.3 g, 0.22 mols) and methanesulfonyl chloride (14.7 g, 0.123 mols), the latter maintained at 0°C, are added within 30 minutes.

After completion of the addition, the mixture is poured into a solution of H_2O (ml 200) and 1N NaOH (20 ml), the phases are separated and the organic layer is washed three times with water (100 ml each), then dried and concentrated to dryness. The residue is added with acetone (200 ml) and 48% hydrobromic acid (5 ml); the resulting solution, having a pH of 3.8, is evaporated under vacuum. The residue is taken up with isopropyl alcohol (80 ml) and kept under stirring at 0 ÷ 5°C for 2 hours. The crystallized product is filtered, washed with cold isopropanol and dried to constant weight.

Yield = 15.5 g (70%)

^{1}H-NMR ($CDCl_3$) 18 (2H, m); 2.37 and 2.55 (2H; AB); 2.71 and 2.75 (6H, S); 3.1 (2H, S); 5.2 (2H, AB); 7.08 (2H, t); 7.54 (H, S); 7.52 (2H, q); 7.62 (H, d); 7.67 (H, d); 11.5 (H, S)

IR = n (cm-1) = 2700 ($N(CH_3)_2H$+); 2225 (CN); 1225, 1217 (C-F); 1029, 1010 (C-O), 845, 834 (aromatic)

Elemental analysis for $C_{20}H_{22}N_2OFHBr$:

Calculated: C = 59.26%; H = 5.43%; N = 6.91%

Found: C = 59.10%; H = 5.63%; N = 7.18%.

m.p. = 182 – 184°C.

Example 8 (for comparison with example 7)

5-Formyl-[1-(3-dimethylpropyl)-1-(4-fluorophenyl)-1,3-dihydroiso-benzofuran)-oxime (formula II).

A mixture of 96% H_2SO_4 (1 ml) and H_2O (0.7 ml) is added to the solution of the compound of example 6 (2 g, 5.55 mmoles) in toluene (20 ml) and the resulting mixture is heated at 80°C for 1 hour, then poured into

ice-water. The phases are separated; the aqueous phase is adjusted to basic pH with 1 N NaOH, extracted with toluene, dried and concentrated to dryness.

Yield: 1.85 g (97%), HPLC purity = 95%

^{1}H-NMR ($CDCl_3$): 1.5 - 1.7 (2H, m); 2.2 (6H, s); 2.2 (2H, m); 2.4 (2H, t); 5.15 (2H, AB); 7 (2H, t); 7.2 (H, d); 7.35 (H, s); 7.4 (H, d); 7.48 (2H, dd); 8.1 (H, s); 11.5 (H exchanges with D_2O)

IR = n (cm^{-1}) 3180, 2800 (N-OH), 1700 (C=N); 1225 (C-F); 1030, 980 (C-O)

Elemental analysis for $C_{20}H_{23}N_2O_2F$:

Calculated: C = 70.18%: H = 6.72%; N = 8.1%

Found: C = 71.43%; H = 7.02%; N= 7.39%

Example 9 (for comparison with example 7)

1-(3-Dimethylpropyl)-1-(4'-fluorophenyl)-1,3-dihydroisobenzofuran-5-carbonitrile.

The compound of example 7 (0.7 g, 2.04 mmoles) is dissolved in acetic anhydride (4 ml) and refluxed for 30 minutes, distilling off the solvent to obtain a dense residue. This is added with ice (30 g) and 25% NH_4OH to pH 9, extracted with ethyl acetate, washed with water, dried and concentrated to dryness.

The residue is chromatographed over SiO_2 eluting with methylene chloride 90 : methanol 10.

Yield = 0.55 g; HPLC purity = 98%

^{1}H-NMR ($CDCl_3$): 1.3.1.55 (2H, 2m); 215 (6H; S); 2.18 (2H, m), 2.25 (2H, t); 5.15 (2H, AB); 7.05 (2H, t); 7.2 (H; d); 7.4 (2H, dd); 7.5 (H, S); 7.6 (H, d).

IR: n (cm-1) 2225 (CN); 226 (C-F); 1035 (C-O)

Elemental analysis for $C_{20}H_{21}N_2OF$:

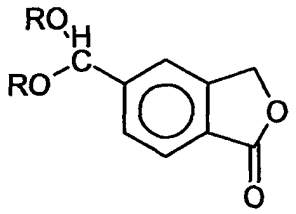
Calculated: C = 74.07%; H = 6.48%; N = 8.1%

Found: C = 72.32%; H = 6.55%; N = 8.29%

CLAIMS

1. A process for the preparation of Citalopram, comprising:

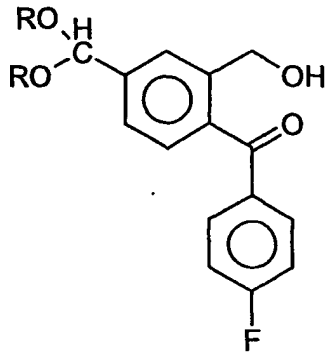
a) the reaction of a compound of formula (VII):



(VII)

wherein R is C_1-C_4 alkyl;

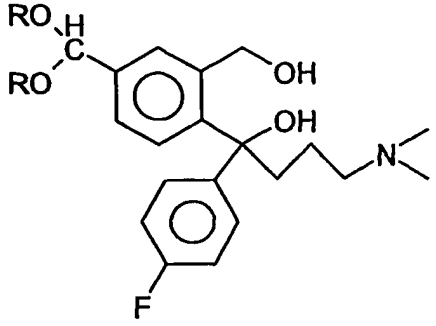
with a fluorobenzyl magnesium halide, to give a compound of formula (VI):



(VI)

wherein R is as defined above;

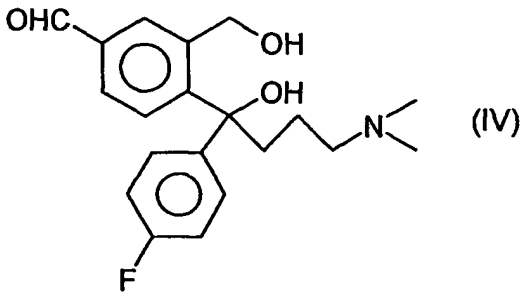
b) the reaction of the compound (VI) with a 3-halomagnesium N,N-dimethylpropylamine to give a compound of formula (V)



(V)

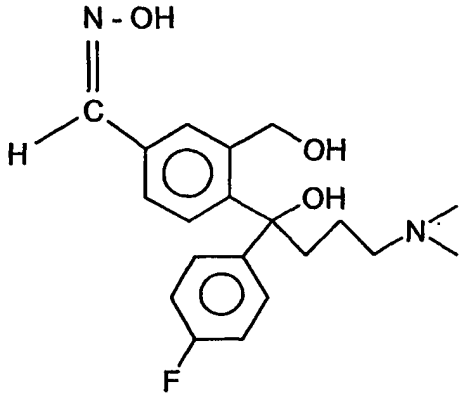
wherein R is as defined above;

c) the acid hydrolysis of the compound of formula (V) to give the compound of formula (IV);



(IV)

d) the reaction with hydroxylamine to give the compound of formula (III):



(III)

e) the conversion of the compound of formula (III) into the compound of formula (I), recovered as base or as a pharmacologically acceptable salt.

2. Process as claimed in claim 1 wherein in step a) 4-fluorobenzyl magnesium bromide is employed.

3. Process as claimed in claim 1 wherein in step b) N,N-dimethylpropylamine magnesium chloride is employed.

4. Process as claimed in claims 1-3 wherein the hydrolysis of intermediate of formula (V) is carried out in a water-alcohol medium by means of inorganic acids.

5. Process as claimed in claims 1-4 wherein the intermediate of formula (IV) is transformed into the compound of formula (III) by reaction with hydroxylamine salts in a water-alcohol medium.

6. Process as claimed in claim 5 wherein hydroxylamine salts are

hydrochloride or sulfate.

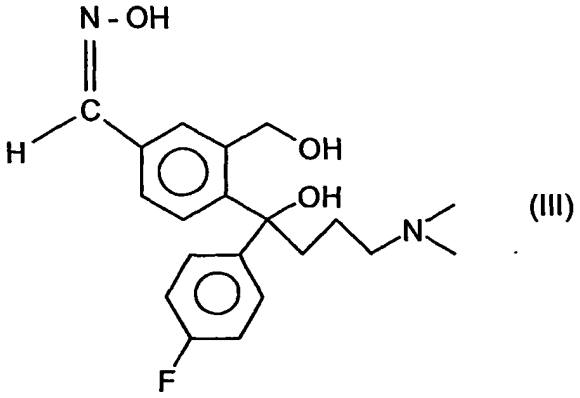
7. Process as claimed in claim 5 wherein the alcohol in the medium is methanol or ethanol.

8. Process as claimed in claims 1-5 wherein the benzofuranic ring closure and the simultaneous transformation of the 5-oxime group to 5-cyano is carried out on the compound of formula (III), by means of methansulfonyl chloride and organic bases.

9. Process as claimed in claim 8 wherein organic bases are triethylamine, dimethylamine or pyridine.

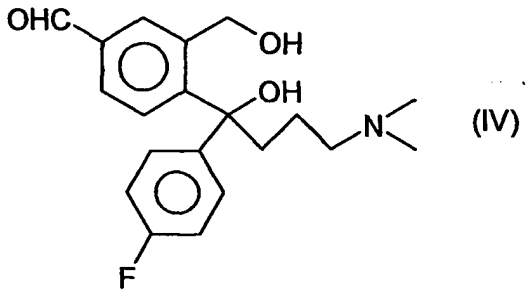
10. Process as claimed in claims 1-9 characterised in that step e) is carried out on the (S) enantiomer of the compound of formula (III).

11. An intermediate of formula (III)



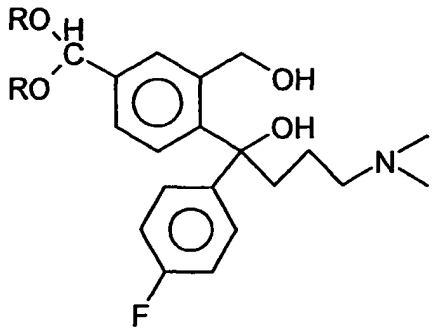
(III)

12. An intermediate of formula (IV).



(IV)

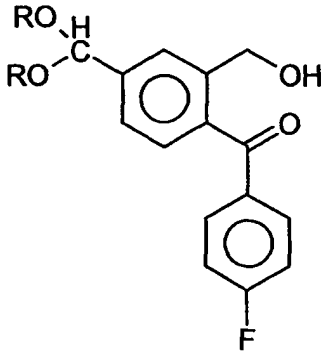
13. An intermediate of formula (V)



(V)

wherein R = C_1-C_4 alkyl.

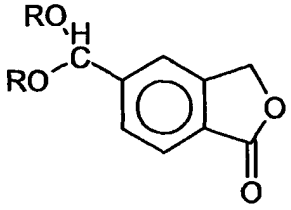
14. An intermediate of formula (VI)



(VI)

wherein R = C_1-C_4 alkyl.

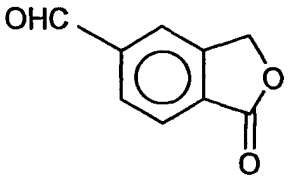
15. An intermediate of formula (VII)



(VII)

wherein R = C_1-C_4 alkyl.

16. An intermediate of formula (VIII)



(VIII)